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(54) Title: BENZOFURAN DERIVATIVES AND THEIR USE AS ANTIBACTERIAL AGENTS

(57) Abstract: The invention relates to novel benzofuran derivatives and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as anti-infectives.

BENZOFURAN DERIVATIVES AND THEIR USE AS ANTIBACTERIAL AGENTS

The present invention relates to novel 2,4-diamino-5- (substituted) pyrimidines, to pharmaceutical compositions containing them, to processes for preparing them and their compositions, to Intermediates for making them and to their use in the treatment of microbial Infections.

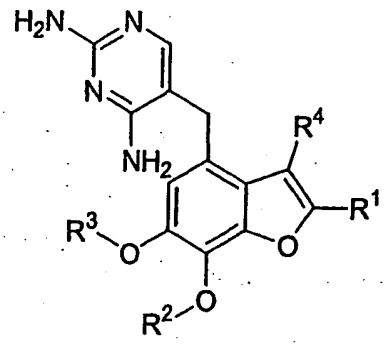
Certain 2,4-diamino-5-benzylpyrimidines have been demonstrated to be potent inhibitors of dihydrofolate reductase (DHFR) which catalyses the reduction of dihydrofolic acid to tetrahydrofolic acid (THFA). This property has been shown frequently to result in useful pharmaceutical properties particularly in the treatment of bacterial infections. Thus, U.K. Patent Specification No. 875,562 discloses inter alia 2,4-diamino-5-benzylpyrimidines wherein the benzyl moiety is substituted by three C_{1-4} alkoxy groups.

Trimethoprim 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine, is specifically disclosed In U.K. Patent No. 875, 562 and is the most active general antibacterial agent amongst the 2,4-diamino-5-benzylpyrimidines known to date. Due to their mode of action, these benzylpyrimidines potentiate the antibacterial activity of the sulphonamides and Trimethoprim has been used extensively over the last decade in human therapy in combination with various sulphonamides, and in particular with sulphamethoxazole, for the treatment of bacterial infections.
European Patent Applications Nos. 81109631.2 and 83104240.3 disclose inter alia also such type of compounds and their use.

It has now been found that a group of novel benzofuran derivatives is more potent than e. g. Trimethoprim and is especially active against Gram positive pathogens like *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis* or *Streptococcus pneumoniae* and at the same time also against Gram negative pathogens like *Haemophilus influenzae*, *Escherichia coli*, *Klebsiella pneumoniae* or *Proteus vulgaris*. The compounds proved to be especially potent against respiratory tract pathogens.

Therefore, the present invention relates to novel compounds of the general formula I

Formula I



I

wherein

R^1 represents straight or branched chain lower alkyl with 2 to 6 carbon atoms; cycloalkylmethyl with 3 to 6 carbon atoms; arylmethyl or heteroarymethyl, the aryl and heteroaryl group may be mono-, di- or tri- substituted with halogen, amino, lower alkyloxy, lower alkylcarbonylamino, arylcarbonylamino, whereby these substituents may be the same or different; straight or branched chain lower alkylcarbonyl with up to 6 carbon atoms; cycloalkylcarbonyl with 3 to 6 carbon atoms; cycloalkylhydroxymethyl with 3 to 6 carbon atoms; arylcarbonyl, the aryl group may be mono-, di or tri- substituted with halogen, amino, lower alkyloxy, lower alkylcarbonylamino, arylcarbonylamino, whereby these substituents may be the same or different; arylhydroxymethyl, the aryl group may be mono-, di- or tri- substituted with halogen, amino, lower alkyloxy, lower alkylcarbonylamino, arylcarbonylamino, whereby these substituents may be the same or different; straight or branched chain lower alkenyl with 2 to 6 carbon atoms;

R^2 and R^3 independently represent hydrogen; lower alkyl with 1 to 3 carbon atoms; or together a lower alkylene group with 1 to 3 carbon atoms bridging the oxygen atoms and forming a five, six or seven membered ring;

R^4 represents hydrogen; straight or branched chain lower alkyl with 1 to 4 carbon atoms;

and pharmaceutically acceptable salts and N-oxides thereof.

In the definitions of the general formula I – if not otherwise stated – the expression lower means straight and branched chain groups with either one or two to six or three carbon atoms, preferably 1 to 3 carbon atoms. Examples of lower alkyl and lower alkoxy groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.- butyl, tert.-butyl, pentyl, hexyl, methoxy, ethoxy, propoxy, butoxy, iso-butoxy, sec.-butoxy and tert.-butoxy. Lower alkylene groups as bridging two oxygen atoms are preferably methylen(-dioxy), ethylen(-dioxy) and propylen(-dioxy) groups and forming in this way a five-, six- or seven-membered ring. Examples of lower alkanoyl-groups are acetyl, propanoyl and butanoyl. Lower alkenylen means e.g.vinylen, propenylen and butenylen. Lower alkenyl and lower alkynyl means groups like ethylen, propylen, butylen, 2-methyl-propenyl, and ethinylen, propinylen, butinylen, pentinylen, 2-methyl-pentinylen etc. Lower alkenyloxy means allyloxy, vinyloxy, propenyloxy and the like. The expression ***cycloalkyl*** means a saturated cyclic hydrocarbon ring with 3 to 6 carbon atoms , e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, which may be substituted with lower alkyl, hydroxy-lower alkyl, amino-lower alkyl, lower alkoxy-lower alkyl and lower alkenylen groups. The expression ***heteroaryl*** means six-membered aromatic rings containing one to four nitrogen atoms, benzofused six-membered aromatic rings containing one to three nitrogen atoms, five-membered aromatic rings containing one oxygen or one nitrogen or one sulfur atom, benzo- fused five-membered aromatic rings containing one oxygen or one nitrogen or one sulfur atom, five membered aromatic rings containig an oxygen and nitrogen atom and benzo fused derivatives thereof, five membred aromatic rings containing a sulfur and a nitrogen atom and benzo fused derivatives thereof, five- membered aromatic rings containing two nitrogen atoms and benzo fused derivatives thereof, five membered aromatic rings containing three nitrogen atoms and benzo fused derivatives thereof or the tetrazolyl ring e.g. furanyl, thienyl, pyrrolyl, pyridinyl, indolyl, quinolinyl, isoquinolinyl, imidazolyl, triazinyl, thiazinyl, thiazolyl, isothiazolyl, pyridazinyl, oxazolyl, isoxazolyl, etc. whereby such rings may be substituted with lower alkyl, lower alkenyl, amino, amino-lower alkyl, halogen, hydroxy, lower alkoxy, trifluoromethoxy or trifluoromethyl. The expression ***aryl*** represents unsubstituted as well as mono-, di- or tri-substituted aromatic rings with 6 to 10 carbon atoms like phenyl or naphthyl rings which may be substituted with aryl, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy, lower alkenyloxy, lower alkynyl-lower alkyl-oxy, lower alkenylen, lower alkylenoxy, lower alkylenoxy or lower alkylendioxy forming with the phenyl ring a five- or six-membered ring, hydroxy-lower alkyl, hydroxy-lower alkenyl, hydroxy-lower alkyl-lower alkynyl, lower alkyloxy-lower alkyl, lower alkyloxy-lower alkyloxy, trifluoromethyl, trifluoromethoxy, cycloalkyl, hydroxy-cycloalkyl, heterocyclyl, heteroaryl.

Especially preferred compounds are compounds of formula I, wherein R^1 means acetyl; allyl; isopropenyl; 2,2-dimethylpropyl; cyclopropylmethyl; phenacyl or benzyl.

Also especially preferred compounds are compounds of formula I, wherein R^2 and R^3 are methyl or together are a methylen group bridging the oxygen atoms to which they are attached.

Very preferred compounds are compounds of formula I, wherein R^1 is cyclopropylmethyl; 2,2-dimethylpropyl; benzyl or arylmethyl; R^2 and R^3 are both methyl and R^4 is hydrogen.

Most preferred compounds are compounds of formula I, wherein R^1 is cyclopropylmethyl; R^2 and R^3 are both methyl and R^4 is hydrogen; or R^1 is benzyl; R^2 and R^3 are both methyl and R^4 is hydrogen; or R^1 is 2,2-dimethylpropyl; R^2 and R^3 are both methyl and R^4 is hydrogen.

Preferred compounds of the present invention include:

5-[6,7-Dimethoxy-2-(2,2-dimethylpropyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(cyclopropylmethyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(phenylmethyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-((4-methoxyphenyl)methyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-((4-chlorophenyl)methyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-((4-fluorophenyl)methyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(1-naphthylmethyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(2-propenyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-(6,7-Dimethoxy-2-trifluoromethylbenzofuran-4-ylmethyl)pyrimidine-2,4-diamine,

5-(6,7-Dimethoxy-2-phenylbenzofuran-4-ylmethyl)pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(2,2-dimethylpropanoyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(cyclopropylcarbonyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-(6,7-Dimethoxy-2-benzoylbenzofuran-4-ylmethyl)pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(4-methoxybenzoyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(4-chlorobenzoyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(4-fluorobenzoyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(1-naphthoyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(2,2-dimethyl-1-hydroxypropyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(cyclopropyl(hydroxy)methyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(phenyl(hydroxy)methyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-((4-methoxyphenyl)(hydroxy)methyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-((4-chlorophenyl)(hydroxy)methyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-((4-fluorophenyl)(hydroxy)methyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(1-naphthyl(hydroxy)methyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(imidazol-1-ylmethyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(pyrrol-1-ylmethyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(1,2,3,4-tetrahydroquinoline-1-ylmethyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(1,2,3,4-tetrahydroisoquinoline-2-ylmethyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(tetrazol-5-ylmethyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(indol-1-ylmethyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(imidazol-1-ylcarbonyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(pyrrol-1-ylcarbonyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(1,2,3,4-tetrahydroquinoline-1-ylcarbonyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(1,2,3,4-tetrahydroisoquinoline-2-ylcarbonyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(tetrazol-5-ylcarbonyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(indol-1-ylcarbonyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

and pharmaceutically acceptable salts and N-oxides thereof.

The expression pharmaceutically acceptable salts encompasses either salts with inorganic acids or organic acids like hydrohalogenic acids, e.g. hydrochloric or hydrobromic acid; sulfuric acid, phosphoric acid, nitric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, methylsulfonic acid, p-toluolsulfonic acid and the like or in case the compound of formula I is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide etc.

Because of their ability to inhibit Gram positive and Gram negative bacteria, the described compounds can be used for the treatment of diseases which are associated with an infection by such type of pathogens. They are valuable anti-infectives.

The compounds can be administered orally, rectally, parenterally, e.g. by intravenous, intramuscular, subcutaneous, intrathecal or transdermal administration or sublingually or as ophthalmic preparation or administered as aerosol. Examples of applications are capsules, tablets, orally administered suspensions or solutions, suppositories, injections, eye-drops, ointments or aerosols/nebulizers.

Preferred applications are intravenous, intra-muscular, or oral administrations as well as eye drops. The dosage used depends upon the type of the specific active ingredient, the age and the requirements of the patient and the kind of application. Generally, dosages of 0.1 – 50 mg / kg body weight per day are considered. The preparations with compounds of formula I can contain inert or as well pharmacodynamically active excipients like sulphonamides. Tablets or granules, for example, could contain a number of binding agents, filling excipients, carrier substances or diluents.

These compositions may be administered in enteral or oral form e.g. as tablets, dragees, gelatine capsules, emulsions, solutions or suspensions, in nasal form like sprays or rectally in form of suppositories. These compounds may also be administered in intramuscular, parenteral or intraveneous form, e.g. in form of injectable solutions.

These pharmaceutical compositions may contain the compounds of formula I as well as their pharmaceutically acceptable salts in combination with inorganic and/or organic excipients which are usual in the pharmaceutical industry like lactose, maize or derivatives thereof, talcum, stearinic acid or salts of these materials.

For gelatine capsules vegetable oils, waxes, fats, liquid or half-liquid polyols etc. may be used. For the preparation of solutions and syrups e.g. water, polyols, saccharose, glucose etc. are used. Injectables are prepared by using e.g. water, polyols, alcohols, glycerin, vegetable oils, lecithin, liposomes etc. Suppositories are prepared by using natural or hydrogenated oils, waxes, fatty acids (fats), liquid or half-liquid polyols etc.

The compositions may contain in addition preservatives, stabilisation improving substances, viscosity improving or regulating substances, solubility improving substances,

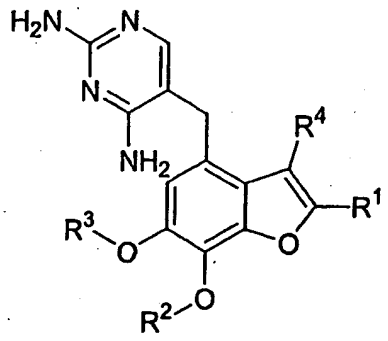
sweeteners, dyes, taste improving compounds, salts to change the osmotic pressure, buffer, anti oxidants etc.

The compounds of formula I may also be used in co-therapy with one or more other therapeutically used classes of antimicrobial substances, for example, β-lactams e.g. penicillins and cephalosporins; glycopeptides; quinolones; tetracyclines; aminoglycosides; macrolides etc.

The dosage may vary within wide limits but should be adapted to the specific situation. In general the dosage given in oral form should daily be between about 3 mg and about 4 g, preferably between about 0.2 g and about 4 g, especially preferred between 0.2 g and 2 g per adult with a body weight of about 70 kg. The dosage should be administered preferably in 1 to 3 doses per day which are of equal weight. As usual children should receive lower doses which are adapted to body weight and age.

The invention also relates to a process for the manufacture of compounds of formula I

Formula I



I

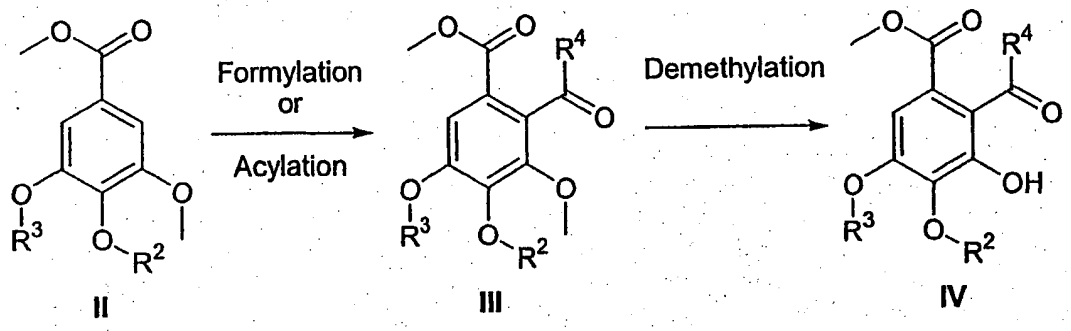
wherein

R^1, R^2, R^3 and R^4 have the meaning given in formula I above,

which process comprises reacting – as depicted in **Scheme 1** – a compound of the general formula **III** (obtained from a gallate derivative **II**: either by Friedel-Crafts acylation, or via a Vilsmeyer aldehyde synthesis (K. Hayashi, K. Tokura, K. Okabe, K. Yamamoto, and K Tawara, *Chem. Pharm. Bull.* **1982**, *30*, 2860-2869), or by formylation with

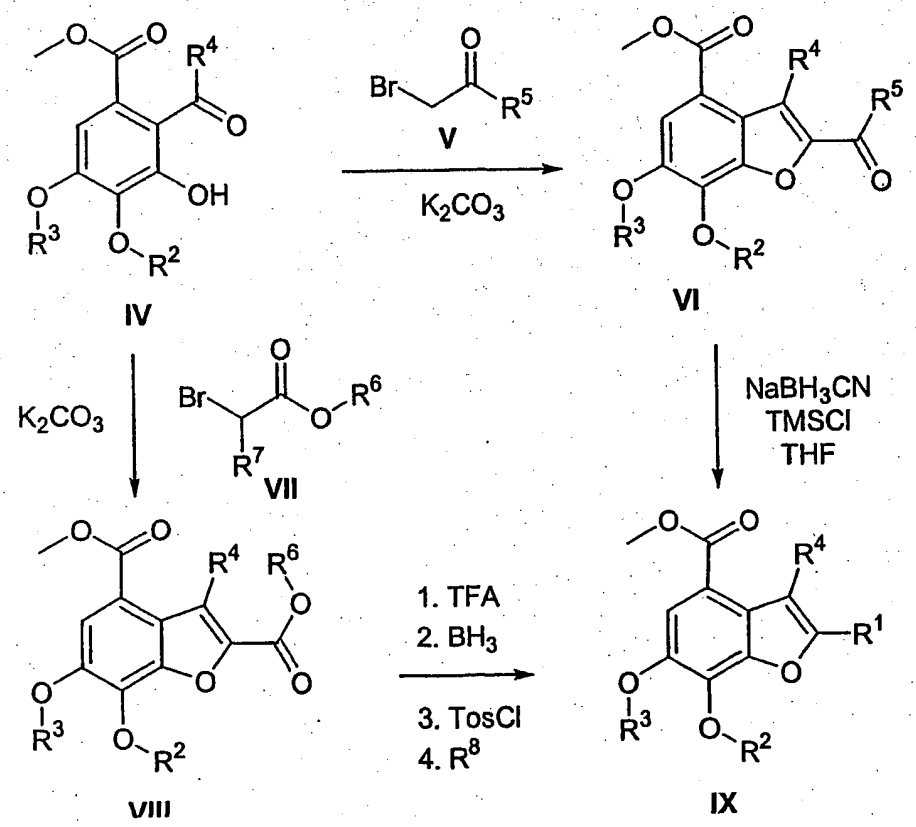
dichloromethoxymethane, see experimental part), with boron trichloride or boron tribromide at temperatures between –70°C and 0°C. The methoxy group adjacent to the acyl group is thereby selectively cleaved, to yield ortho-acyl phenol derivatives of the general formula **IV**:

Scheme 1



Subsequently, the compounds **IV**, wherein R^2, R^3, and R^4 have the meaning given in formula **I** above, are reacted with α-bromomethyl ketones R^5-CO-CH_2Br **V** in the presence of potassium carbonate, to yield 2-acylated benzofuran derivatives **VI** (**Scheme 2**)

Scheme 2



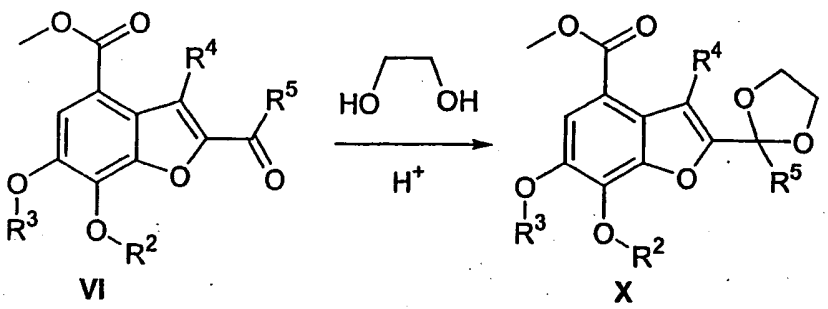
whereby in formula V R^5 represents straight or branched chain lower alkyl with 1 to 5 carbon atoms; cycloalkyl with 3 to 6 carbon atoms; aryl or heteroaryl, the aryl and heteroaryl group may be mono-, di- or tri- substituted with halogen, amino, lower alkyloxy, lower alkylcarbonylamino, arylcarbonylamino, whereby these substituents may be the same or different; straight or branched chain lower alkenyl with 2 to 6 carbon atoms.

The carbonyl group of **VI** can then be removed selectively by reducing it with sodium cyanoborohydride in the presence of trimethylsilyl chloride, to yield the benzofuran ester derivatives **IX**, wherein R^1, R^2, R^3, and R^4 have the meaning given in formula **I**.

Alternatively, benzofurans of the general structure **IX** can be obtained by reacting **IV** with an α-bromo-ester derivative $R^6OCO\text{-}CH(Br)\text{-}R^7$ **VII** (R^6 is *tert*-butyl, and R^7 may be hydrogen or *tert*-butoxycarbonyl), again in the presence of carbonate, to give benzofuran dicarboxylates of the formula **VIII**, whereby R^2, R^3, and R^4 have the meaning given in formula **I**, and R^6 represents the *tert*-butyl group. The latter can be cleaved selectively with trifluoroacetic acid, and may then be reduced preferentially with diborane. The resulting primary alcohol is then converted into a leaving group, e.g. a tosylate, which is then displaced by a nucleophile R^8, such as a nitrogen-containing heteroaromatic moiety.

If the acyl group in formula **VI** (**Scheme 2**) is to be preserved, i.e. if in the final product (formula **I**) R^1 represents an acyl group (cycloalkylcarbonyl, arylcarbonyl etc.), it may be protected as an ethylene ketal, as set forth in structure **X** (**Scheme 3**):

Scheme 3

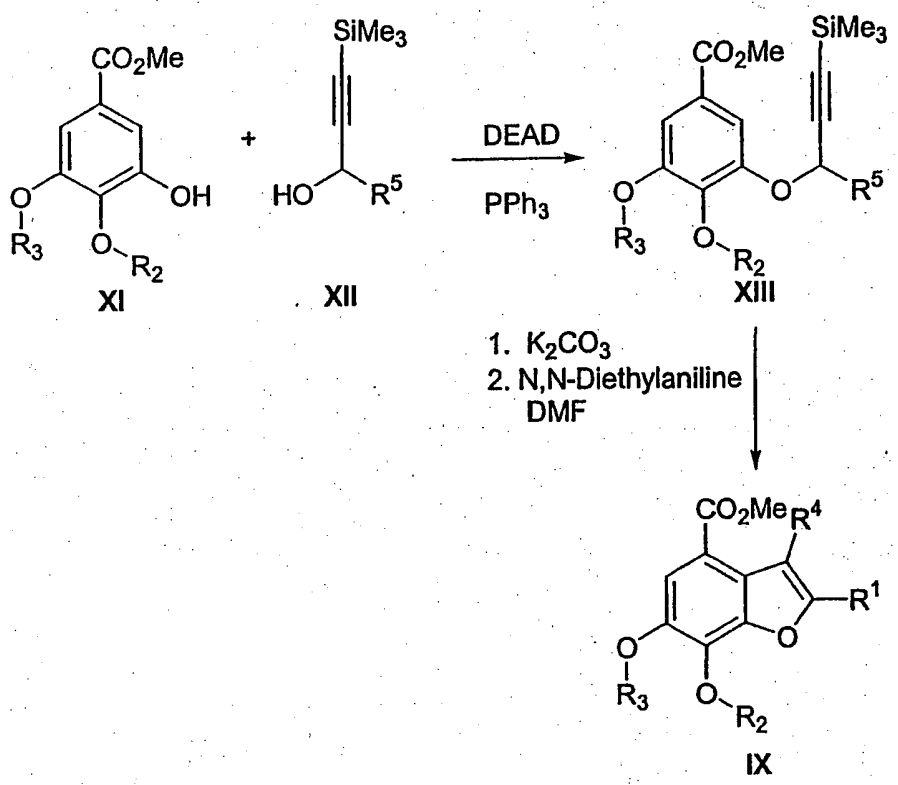


VI **X**

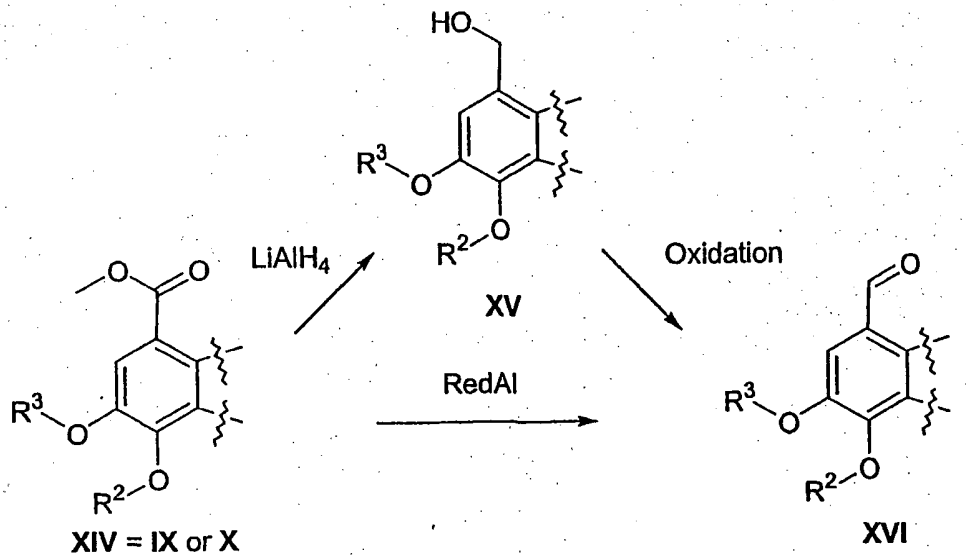
In a third alternative approach described in **Scheme 4**, phenol **XI** (Wipf, P.; Weiner, W.S. *J. Org. Chem.* **1999**, *64*, 5321-5324) is reacted with a propargylic alcohol derivative **XII** under Mitsunobu conditions (diethyl azodicarboxylate and triphenyl phosphine) to afford the phenyl ethers **XIII**. After cleaving off the trimethylsilyl protecting group with potassium

carbonate, the resulting free acetylenes can be rearranged, as described previously (Koch-Pomeranz, U.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 2981-3004), to benzofurans **IX**.

Scheme 4



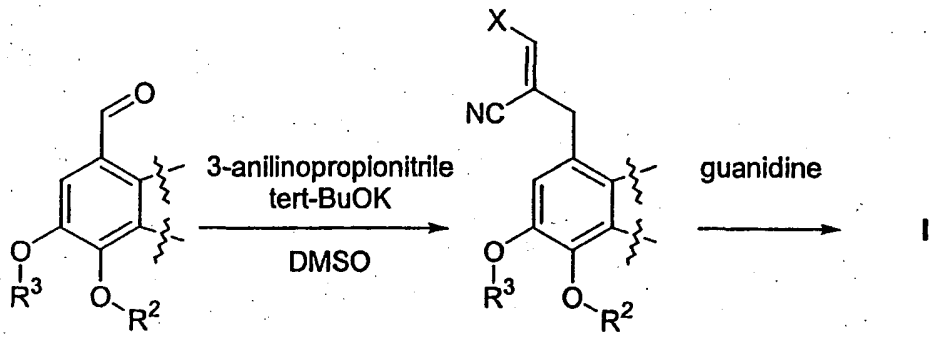
Scheme 5



The manufacturing process then continues as depicted in **Scheme 5**. The ester function of the general substructure **XIV** (consisting of either **IX** or **X**) is reduced to an aldehyde **XVI**, either directly, with an organoaluminum hydride reagent, or in two steps, via the primary alcohol **XV**.

Finally, the aldehyde group is transformed into the diaminopyrimidine ring, employing the standard technology outlined in **Scheme 6**.

Scheme 6



XVI **XVII**

Thus, compounds of formula I can be obtained; if R^1 represents an acyl group, i.e. structure **XVII** has been the intermediate, the final elaboration includes an acid-induced removal of the ketal protecting group.

Examples

General procedure A: Formylation

Under argon at –20°C, to a solution of compound **II** (1.0 eq.) in dry CH_2Cl_2 was added dichloromethylmethyl ether (1.5 eq.). $SnCl_4$ (1.0 eq.) was added dropwise over a period of 30 min, while maintaining the inside temperature at –20°C. After the addition, the mixture was allowed to slowly warm up to room. After disappearance of the starting material (TLC), the reaction mixture was again cooled to –10°C and quenched by slowly addition of $NaHCO_3$. The organic phase was collected, the aqueous phase was extracted with three portions of tert-butyl methyl ether (TBME), the combined organic phases were washed with brine, dried with $MgSO_4$ and the solvents removed under reduced pressure to give compound **III**.

Example 1:

Methyl 2-formyl-3,4,5-trimethoxybenzoate was obtained as a yellow foam (39.0 g, 90%, 85% HPLC purity) by reacting methyl 3,4,5-trimethoxybenzoate (36.0 g) with dichloromethylmethyl ether (27.0 g, 1.5 eq.) and $SnCl_4$ (41.5 g, 1.0 eq). The product, which is rather unstable, was directly used for the next step.

MNR $CDCl_3$ 300 MHz δ in ppm J in Hz: 10.28 (s, 1H, COH), 6.93 (s, 1H, Ar), 3.96 (s, 3H, OMe), 3.93 (s, 3H, OMe), 3.89 (s, 6H, 2 OMe).

General procedure B: Demethylation

Under argon at -10°C, to a solution of compound **III** (1 eq.) in methylene chloride, BBr_3 (0.5 eq.) was added over a period of 20 min, such that the temperature was not exceeding 0°C. The mixture was stirred at 0°C, until disappearance of the starting material. The reaction mixture was poured into ice-water and the aqueous layer was extracted with two portions of TBME. The combined organic phases were washed with water, dried with $MgSO_4$, and the solvents evaporated under reduced pressure to give compound **IV**.

Example 2:

Methyl 2-formyl-3-hydroxy-4,5-dimethoxy-benzoate (36.8 g, 98%, 88% HPLC purity) was obtained as a white crystalline compound by reacting methyl 2-formyl-3,4,5-trimethoxybenzoate (39.5 g) with BBr_3 (7.5 ml, 0.5 eq.).

MNR $CDCl_3$ 300 MHz δ in ppm J in Hz: 12.28 (s, 1H, OH), 10.26 (s, 1H, COH), 6.57 (s, 1H, Ar), 4.01 (s, 3H, OMe), 3.98 (s, 6H, 2 OMe).

General procedure C: Synthesis of benzofurans

Under argon, compound **IV** (1 eq.) was dissolved in DMF or toluene (Fluka on 4Å Mol. sieve), K_2CO_3 powder (2.4 eq.) and in some cases tetrabuthylammonium bromide (0.1 eq.) was added. After 10 min stirring at r.t., a bromoketone**V**, a bromomalonic ester **VII** or a α-bromoester **VII** (1.2 to1.9 eq.) was added as well as some 4Å Mol. sieves. The reaction was stirred 3h to 24h at 110°C. The reaction mixture was filtrated and the solvent evaporated. The residual brown oil was dissolved in CH_2Cl_2 and washed with water and brine. The organic layer was dried with $MgSO_4$, the solvent evaporated to give the compound **VI** or **VIII**.

Example 3:

6,7-Dimethoxy-2-cyclopropylcarbonyl-benzofuran-4-carboxylic acid methyl ester (128 mg, 59%) was obtained as a yellow solid after crystallisation from ethyl acetate by reacting methyl 2-formyl-3-hydroxy-4,5-dimethoxy-benzoate (170 mg, 0.70 mmol) with 2-bromo-1-cyclopropylethanone (0.138 g, 0.849 mmol) (which was previously obtained from the reaction of 1-cyclopropyl-vinyloxitrimethylsilane with N-bromosuccinimide), K_2CO_3 (170 mg, 1.7 eq.) and tetrabuthylammonium bromide (27 mg, 0.07 mmol)

MNR $CDCl_3$ 300 MHz δ in ppm J in Hz: 7.98 (s, 1H, Ar), 7.68 (m, 1H, Ar), 4.28 (s, 3H, OMe), 3.93 (s, 3H, OMe), 3.92 (s, 3H, OMe), 2.72-2.55 (m, 1H), 1.29-1.25 (m, 2H), 1.09-1.04 (m, 2H).

Example 4:

6,7-Dimethoxy-2-phenylcarbonyl-benzofuran-4-carboxylic acid methyl ester (1.1 g, 56%) was obtained as a yellow solid by reacting Methyl 2-formyl-3-hydroxy-4,5-dimethoxy-benzoate (1.5 g, 6.24 mmol) with K_2CO_3 powder (2.07 mg, 14.97 mmol) and phenacyl bromide (2.36 mg, 11.86 mmol)

MNR $CDCl_3$ 300 MHz δ in ppm J in Hz: 8.04 (s, 1H, Ar), 7.74 (s, 1H, Ar), 7.68-7.54 (m, 5H, Ar), 4.37 (s, 3H, OMe), 4.00 (s, 3H, OMe), 3.97 (s, 3H, OMe).

MP: 116-120°C

Example 5:

6,7-Dimethoxy-2-(2,2-dimethylpropanoyl)-benzofuran-4-carboxylic acid methyl ester (182 mg, 57%) was obtained as a yellow solid by reacting methyl 2-formyl-3-hydroxy-4,5-dimethoxy-benzoate (250 mg, 1.04 mmol) with K_2CO_3 powder (338 mg, 2.44 mmol) and 1-bromopinacolon (265 µl, 1.96 mmol).

MNR $CDCl_3$ 300 MHz δ in ppm J in Hz: 8.04 (s, 1H, Ar), 7.72 (s, 1H, Ar), 4.35 (s, 3H, OMe), 3.98 (s, 3H, OMe), 3.96(s, 3H, OMe), 1.45 (s, 9H, tert-Bu)

MP 104-108°C

Example 6:

6,7-Dimethoxy-2-tert-butoxycarbonyl-benzofuran-4-carboxylic acid methyl ester (100 mg, 37%) was obtained as a yellow solid by reacting methyl 2-formyl-3-hydroxy-4,5-dimethoxy-benzoate (200 mg, 0.83 mmol) with K_2CO_3 powder (172 mg, 1.24 mmol), tetrabuthylammonium bromide (27 mg, 0.08 mmol) and bromomalonicacid tert-butyl ester (294 mg, 1.00 mmol).

General procedure D: Reduction of the ketone

Under argon at 0°C, to a solution of the ketone **VI** (1 eq.) in freshly distilled THF trimethylsilyl chloride (10 eq.), 4Å Mol sieve powder and then sodium cyanoborohydride (10 eq.) were added. The reaction was complete after stirring it for 5h to 24 h at r.t. Dichloromethane was added to the reaction mixture, which was then filtrated through celite. After several washings of the residue with CH_2Cl_2, the filtrate was washed with water and brine, dried with $MgSO_4$ and the solvents evaporated to give compound **IX**.

Example 7:

6,7-Dimethoxy-2-cyclopropylmethyl-benzofuran-4-carboxylic acid methyl ester (94 mg, 90%) was obtained as a glassy solid by reacting trimethylsilyl chloride (46 µl, 3.61 mmol) and sodium cyanoborohydride (240 mg, 3.61 mmol).

MS ESI: 291 (M+H)

Example 8:

6,7-Dimethoxy-2-phenylmethyl-benzofuran-4-carboxylic acid methyl ester (186 mg, 95%) was obtained as a glassy solid, after purification by flash chromatography (Rf 0.66, 3:2, hexane/ethyl acetate) by reacting 6,7-dimethoxy-2-phenylcarbonyl-benzofuran-4-

carboxylic acid methyl ester (200 mg, 0.588 mmol) with sodium cyanoborohydride (370 mg, 5.88 mmol) and trimethylsilyl chloride (743 ml, 5.88 mmol).

MS ESI+: 365 (M+K), 349 (M+Na), 327 (M+H), 295 (M-OMe)

MNR $CDCl_3$ 300 MHz δ in ppm J in Hz: 7.56 (s, 1H, Ar), 7.33-7.26 (m, 5H, Ar), 6.91 (s, 1H, Ar), 4.24 (s, 3H, OMe), 4.13 (s, 2H, CH_2Ar), 3.93 (s, 3H, OMe), 3.91 (s, 3H, OMe).

Example 9:

6,7-Dimethoxy-2-(2,2-dimethylpropyl)-benzofuran-4-carboxylic acid methyl ester (180 mg, 94%) was obtained as a glassy solid by reacting 6,7-dimethoxy-2-(2,2-dimethylpropanoyl)-benzofuran-4-carboxylic acid methyl ester (200 mg, 0.62 mmol) with sodium cyanoborohydride (392 mg, 6.24 mmol) and trimethylsilyl chloride (789 µl, 6.24 mmol).

MNR $CDCl_3$ 300 MHz δ in ppm J in Hz: 7.57 (s, 1H, Ar), 6.92 (s, 1H, Ar), 4.29 (s, 3H, OMe), 3.95 (s, 3H, OMe), 3.94(s, 3H, OMe), 2.66 (s, 2H, CH_2), 1.03 (s, 9H, tert-Bu)

General procedure E: Alternative route to obtain benzofuran derivatives IX

Compound **XI** (1 eq.) was reacted with compound **XII** (1 eq.) (obtained by sodium borohydride reduction of the corresponding ketone) as described previously (Wipf, P.; Weiner, W.S. *J. Org. Chem.* 1999, *64*, 5321-5324) to give compound **XIII**.

Example 10:

3-(1-Cyclopropyl-trimethylsilylprop-2-ynyloxy)-4,5-dimethoxy-benzoic acid methyl ester was obtained as a colorless oil in 60% yield from 1-cyclopropyl-3-(trimethylsilyl)prop-2yn-1-ol. The same compound can also be obtained by a copper-1 (CuCl)-catalyzed process as described by Godfrey et al.(Godfrey Jr., J.D. et al, *Tetrahedron Lett.* 1994, *35*, 6405-6408).

MS: M^+ 362

Ether **XIII** (1 eq.), K_2CO_3 (3 eq.) and KF (3 eq.) were dissolved in methanol. The mixture was stirred and the reaction was monitored by TLC. After 25 minutes the reaction was complete and the mixture was partitioned between of water and a mixture of hexane/ethyl acetate 4:1. The layers were separated, the aqueous layer was washed three times with of hexane/ethyl acetate 4:1. The organic lay rs were combined and evaporated to give the resulting acetylene which was used directly for the next step.

Example 11:

3-(1-Cyclopropyl-prop-2-ynyloxy)-4,5-dimethoxy-benzoic acid methyl ester (17.5 g, 71 %) was obtained as a white solid by crystallization from hexane/ether by reacting 3-(1-cyclopropyl-trimethylsilylprop-2-ynyloxy)-4,5-dimethoxy-benzoic acid methyl ester (30.87 g, 80 mmol) with K_2CO_3 (30 g) and KF (30 g) 17.5 g, 60.4 mmol, 71 %.
mp. 93-94 °C.

The acetylene previously obtained (1 eq.) was dissolved in DMF (tech.) containing 5% N,N-diethylaniline and the reaction mixture was stirred for 2h at 150°C. After work-up and crystallisation from ether the compound **IX** was obtained.

Example 12:

6,7-Dimethoxy-2-cyclopropylmethyl-benzofuran-4-carboxylic acid methyl ester (50%) was obtained as white-red crystals by reacting in an intramolecular fashion 3-(1-cyclopropyl-prop-2-ynyloxy)-4,5-dimethoxy-benzoic acid methyl ester (88 g, 0.316 mol)
NMR $CDCl_3$ 300 MHz δ in ppm J in Hz: 7.57 (s, 1H, Ar), 7.00 (m, 1H, Ar), 4.28 (s, 3H, OMe), 3.95 (s, 3H, OMe), 3.94 (s, 3H, OMe), 2.70 (d, 2H, J = 6.6), 1.95-1.75 (m, 1H), 0.62-0.59 (m, 2H), 0.29-0.25 (m, 2H).

General procedure F: Reduction of the ester to alcohol

Under argon, ester **XIV** (1 eq.) was dissolved in THF freshly distilled and treated with $LiAlH_4$ (3 eq.) The reaction was stirred at 60°C for 2h until disappearance of the starting material. The reaction was quenched with 0.5 N HCl, the white precipitate filtrated and washed with ether. The organic layer was dried with $MgSO_4$ and the solvents evaporated to give the alcohol **XV**.

Example 13:

(6,7-Dimethoxy-2-phenylmethyl-benzofuran-4-yl)-methanol (82 mg, 90%) was obtained by reacting 6,7-dimethoxy-2-phenylmethyl-benzofuran-4-carboxylic acid methyl ester (100 mg, 0.30 mmol) with $LiAlH_4$ (33 mg, 0.91 mmol).
MS ESI: 321 (M+Na)

General procedure G: Oxidation of the alcohol to aldehyde

Under argon, alcohol **XV** (1 eq.) was dissolved in dichloromethane and MnO_2(10 eq.) was added. The reaction mixture was stirred 3h at r.t. and filtrated over celite. The celite was washed with excess of CH_2Cl_2, the solvent evaporated to give the aldehyde **XVI**.

Example 14:

6,7-Dimethoxy-2-phenylmethyl-benzofuran-4-carbaldehyde (119 mg, 62%) was obtained as an oil by reacting (6,7-dimethoxy-2-phenylmethyl-benzofuran-4-yl)-methanol (192 mg, 1.29 mmol) with MnO_2 (1.121 g, 12.90 mmol)

General procedure H: Reduction of the ester to the aldehyde

Under argon at 0°C, to a solution of sodium dihydro-bis(2-methoxyethoxy)-aluminate (Red Al, ca. 3.5 M in toluene) (3.1 eq.) in toluene (over 4Å Mol. sieve) was added dropwise, during 30 min morpholine (3.4 eq.) in toluene. The resulting solution was stirred for 30 min and was slowly added at –30 °C to a solution of the ester **XIV** (1 eq.) in toluene. The reaction mixture was then stirred for 4h at –15°C and quenched by addition of 3N NaOH and stirred until it reached r.t. The reaction mixture was then diluted with ice water and extracted with toluene. The organic layer was washed with water, dried over $MgSO_4$ and the solvent evaporated to give compound **XVI**.

Example 15:

6,7-Dimethoxy-2-cyclopropylmethyl-benzofuran-4-carbaldehyde (1.16 g, 66%) was obtained as light yellow crystals after crystallisation in 5:1 ethyl acetate/hexane by reacting sodium dihydro-bis(2-methoxyethoxy)-aluminate (Red Al, ca. 3.5M in toluene) (6.5 ml, 22.6 mmol) with morpholine (2.1 ml, 24.0 mmol) and 6,7-dimethoxy-2-cyclopropylmethyl-benzofuran-4-carboxylic acid methyl ester (2.05 g, 7.0 mmol)

MNR $CDCl_3$ 300 MHz δ in ppm J in Hz: 10.06 (s, 1H, COH), 7.32 (s, 1H, Ar) 7.51 (s, 1H, Ar), 4.35 (s, 3H, OMe), 3.97 (s, 3H, OMe), 2.72 (d, 2H, J = 7.1), 1.19-1.17 (m, 1H), 0.64-0.60 (m, 2H), 0.29-0.27 (m, 2H).

MP 44-46°C

Example 16:

6,7-Dimethoxy-2-(2,2dimethlypropyl)-benzofuran-4-carbaldehyde (115 mg, 80%) was obtained as an oil from the reaction of sodium dihydro-bis(2-methoxyethoxy)-aluminate (Red Al, ca. 3.5M in toluene) (500 µl, 1.62 mmol) with morpholine (159 µl, 1.83 mmol) and

6,7-dimethoxy-2-(2,2dimethlypropyl)-benzofuran-4-carboxylic acid methyl ester (160 mg, 0.522 mmol).

General procedure I: Coupling with anilinopropionitrile

Under argon at 10°C, the aldehyde **XVI** (1 eq.) was dissolved in DMSO (25 ml) and freshly crystallized 3-anilinopropionitrile (1.1 eq.) was added. Potassium tert-butoxide (1.15 eq.) was added portionwise to the reaction mixture. The solution was stirred at 10°C for 1h and at r.t. for 3h. The reaction mixture was poured into ice-water and extracted 3 times with ethyl acetate. The organic layer was washed with water and dried over $MgSO_4$. The solvents were evaporated to give compound **XVII**.

Example 17:

3-Anilino-2-(6,7-dimethoxy-2-cyclopropylmethyl-benzofuran-4-ylmethyl)-acrylonitrile (1.87 g, 49%) was obtained after purification by flash chromatography 2:3 ethyl acetate/hexane to as a yellow oil from the reaction of 6,7-dimethoxy-2-cyclopropylmethyl-benzofuran-4-carbaldehyde (2.6 g, 9.9 mmol) with 3-anilinopropionitrile (1.44 g, 10.9 mmol) and potassium tert-butoxide (1.28 g, 11.5 mmol)

Example 18:

3-Anilino-2-(6,7-dimethoxy-2-phenylmethyl-benzofuran-4-ylmethyl)-acrylonitrile (88 mg, 53%) was obtained after purification by flash chromatography (2:3 ethyl acetate/hexane) as a yellow oil by reacting of 6,7-dimethoxy-2-phenylmethyl-benzofuran-4-carbaldehyde (119 mg, 0.40 mmol) with 3-anilinopropionitrile (58 mg, 0.44 mmol) and potassium tert-butoxide (52 mg, 0.46 mmol)

MS ESI: 423 (M-H)

Example 19:

3-Anilino-2-(6,7-dimethoxy-2-(2,2dimethlypropyl)-benzofuran-4-ylmethyl)-acrylonitrile (91 mg, 54%) was obtained after purification by flash chromatography (2:3 ethyl acetate/hexane) as a yellow oil by reacting 6,7-dimethoxy-2-(2,2dimethlypropyl)-benzofuran-4-carbaldehyde (115 mg, 0.42 mmol) with 3-anilinopropionitrile (60 mg, 0.46 mmol) and potassium tert-butoxide (54 mg, 0.48 mmol)

MS ESI: 427 (M+Na)

General procedure J: Cyclisation with guanidine

Under argon, to a solution of guanidine hydrochloride (3 eq.) in potassium tert-butoxide (3 eq.) were added and stirred for 15 min. The fine precipitate was filtrated through celite under argon and the filtrate was added to a solution of compound **XVII** (1 eq.) in ethanol. The reaction mixture was stirred under reflux conditions for 8h. After cooling the reaction to r.t and then to -20°C compound **I** precipitated.

Example 20:

5-(6,7-Dimethoxy-2-cyclopropylmethyl-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (1.16 g, 96%) was obtained as a white-yellow precipitate by reacting guanidine hydrochloride (1.37 g, 14.44 mmol), potassium tert-butoxide (1.62 g, 14.44 mmol) and 3-anilino-2-(6,7-dimethoxy-2-cyclopropylmethyl-benzofuran-4-ylmethyl)acrylonitrile (1.87 g, 4.81 mmol)

MNR CD_3OD 500 MHz δ in ppm J in Hz: 6.95-7.35 (m, 1H, Ar), 6.78 (s, 1H, Ar) 6.44 (s, 1H, Ar), 4.03 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.81 (s, 2H, CH_2), 2.66 (d, 2H, J = 6.8), 1.14-1.04 (m, 1H), 0.59-0.54 (m, 2H), 0.28-0.25 (m, 2H).

MS ISP: 397 (M+Na, 25%), 355 (M+H, 100%).

HPLC purity RP C_{18} Dicovery: 98%

Example 21:

5-(6,7-Dimethoxy-2-phenylmethyl-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (20 mg, 36%) was obtained as a white-yellow precipitate by reacting guanidine hydrochloride (40 mg, 0.42 mmol), potassium tert-butoxide (47 mg, 0.42 mmol) and 3-anilino-2-(6,7-dimethoxy-2-phenylmethyl-benzofuran-4-ylmethyl)-acrylonitrile (59 mg, 0.14 mmol)

MS ESI: 391 (M+H)

HPLC purity RP C_{18} Dicovery: 97%

Example 22:

5-(6,7-Dimethoxy-2-(2,2-dimethlypropyl)-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (28 mg, 33%) was obtained as a white-yellow precipitate by reacting guanidine hydrochloride (64 mg, 0.67 mmol), potassium tert-butoxide (75 mg, 0.67 mmol) and 3-anilino-2-(6,7-dimethoxy-2-(2,2-dimethlypropyl)-benzofuran-4-ylmethyl)-acrylonitrile (91 mg, 0.22 mmol)

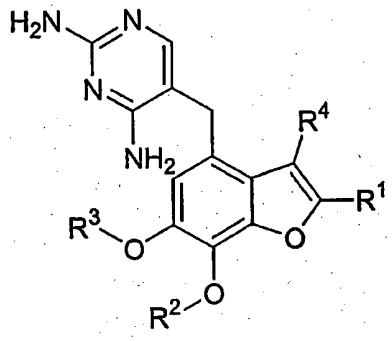
MS ESI: 371 (M+H)

HPLC purity RP C_{18} Dicovery: 99%

Claims

1. Compounds of the general formula I

Formula I



I

wherein

R^1 represents straight or branched chain lower alkyl with 2 to 6 carbon atoms; cycloalkylmethyl with 3 to 6 carbon atoms; arylmethyl or heteroarymethyl, the aryl and heteroaryl group may be mono-, di- or tri- substituted with halogen, amino, lower alkyloxy, lower alkylcarbonylamino, arylcarbonylamino, whereby these substituents may be the same or different; straight or branched chain lower alkylcarbonyl with up to 6 carbon atoms; cycloalkylcarbonyl with 3 to 6 carbon atoms; cycloalkylhydroxymethyl with 3 to 6 carbon atoms; arylcarbonyl, the aryl group may be mono-, di or tri- substituted with halogen, amino, lower alkyloxy, lower alkylcarbonylamino, arylcarbonylamino, whereby these substituents may be the same or different; arylhydroxymethyl, the aryl group may be mono-, di- or tri- substituted with halogen, amino, lower alkyloxy, lower alkylcarbonylamino, arylcarbonylamino, whereby these substituents may be the same or different; straight or branched chain lower alkenyl with 2 to 6 carbon atoms;

R^2 and R^3 independently represent hydrogen; lower alkyl with 1 to 3 carbon atoms; or together a lower alkylene group with 1 to 3 carbon atoms bridging the oxygen atoms and forming a five, six or seven membered ring;

R^4 represents hydrogen; straight or branched chain lower alkyl with 1 to 4 carbon atoms,

and pharmaceutically acceptable salts and N-oxides thereof.

2. Compounds of formula I, wherein R^1 represents acetyl; allyl; isopropenyl; 2,2-dimethylpropyl; cyclopropylmethyl; phenacyl or benzyl.

3. Compounds of formula I, wherein R^2 and R^3 represent methyl or together represent a methylen group bridging the oxygen atoms to which they are attached.

4. Compounds of formula I, wherein R^1 represents cyclopropylmethyl; 2,2-dimethylpropyl; benzyl or arylmethyl; R^2 and R^3 both represent methyl and R^4 represents hydrogen.

5. Compounds of formula I, wherein R^1 represents cyclopropylmethyl; R^2 and R^3 represent both methyl and R^4 represents hydrogen; or R^1 represents benzyl; R^2 and R^3 represent both methyl and R^4 represents hydrogen; or R^1 represents 2,2-dimethylpropyl; R^2 and R^3 represent both methyl and R^4 represents hydrogen.

6. The compounds according to any one of claims 1 to 5

5-[6,7-Dimethoxy-2-(2,2-dimethylpropyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(cyclopropylmethyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(phenylmethyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-((4-methoxyphenyl)methyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-((4-chlorophenyl)methyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-((4-fluorophenyl)methyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(1-naphthylmethyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(2-propenyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-(6,7-Dimethoxy-2-trifluoromethylbenzofuran-4-ylmethyl)pyrimidine-2,4-diamine,

5-(6,7-Dimethoxy-2-phenylbenzofuran-4-ylmethyl)pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(2,2-dimethylpropanoyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(cyclopropylcarbonyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-(6,7-Dimethoxy-2-benzoylbenzofuran-4-ylmethyl)pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(4-methoxybenzoyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(4-chlorobenzoyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(4-fluorobenzoyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(1-naphthoyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(2,2-dimethyl-1-hydroxypropyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(cyclopropyl(hydroxy)methyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(phenyl(hydroxy)methyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-((4-methoxyphenyl)(hydroxy)methyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-((4-chlorophenyl)(hydroxy)methyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-((4-fluorophenyl)(hydroxy)methyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(1-naphthyl(hydroxy)methyl)-benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(imidazol-1-ylmethyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(pyrrol-1-ylmethyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(1,2,3,4-tetrahydroquinoline-1-ylmethyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(1,2,3,4-tetrahydroisoquinoline-2-ylmethyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(tetrazol-5-ylmethyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(indol-1-ylmethyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(imidazol-1-ylcarbonyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(pyrrol-1-ylcarbonyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(1,2,3,4-tetrahydroquinoline-1-ylcarbonyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(1,2,3,4-tetrahydroisoquinoline-2-ylcarbonyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(tetrazol-5-ylcarbonyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

5-[6,7-Dimethoxy-2-(indol-1-ylcarbonyl)benzofuran-4-ylmethyl]pyrimidine-2,4-diamine,

and pharmaceutically acceptable salts and N-oxides thereof.

7. Pharmaceutical compositions for the treatment of infections containing a compound of any one of claims 1 to 6 and usual carrier materials and adjuvants.

8. Pharmaceutical compositions for the treatment of infections caused by Gram positive and Gram negative pathogens, containing a compound of any one of claims 1 to 6 and usual carrier materials and adjuvants.

9. The compounds of any one of the claims 1 to 6 for use as medicaments for the treatment of infections.

10.The compounds of any one of the claims 1 to 6 for use as medicaments for the treatment of infections caused by Gram positive and Gram negative pathogens.

11.The use of one or more compounds of any one of claims 1 to 6 as active ingredients for the production of pharmaceutical compositions for the treatment of infections.

12.The use of one or more compounds of any one of claims 1 to 6 as active ingredients for the production of pharmaceutical compositions for the treatement of infections caused by Gram positive and Gram negative pathogens.

13. A process for the manufacture of pharmaceutical compositions for the treatment of infections containing one or more compounds as claimed in any one of claims 1 to 6 as active ingredients which process comprises mixing one or more active ingredient with pharmaceutically acceptable excipients in a manner known per se.

14. A process for the manufacture of pharmaceutical compositions for the treatment of infections caused by Gram positive and Gram negative pathogens containing one or more compounds as claimed in any one of claims 1 to 6 as active ingredients which process comprises mixing one or more active ingredient with pharmaceutically acceptable excipients in a manner known per se.

15. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/07357

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/06 A61K31/505 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 096 214 A (WELLCOME) 21 December 1983 (1983-12-21) cited in the application page 14, paragraph 3; claims; examples 25,27	1-15
Y	US 5 773 446 A (MASCIADRI) 30 June 1998 (1998-06-30) column 6, line 65 -column 7, line 30; claims; examples	1-15
Y	US 4 438 267 A (DALUGE ET. AL.) 20 March 1984 (1984-03-20) column 1, line 12 - line 65; claims; examples	1-15

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 March 2001	21/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Helps, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/07357

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	GB 875 562 A (WELLCOME) 23 August 1961 (1961-08-23) cited in the application claims; examples	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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